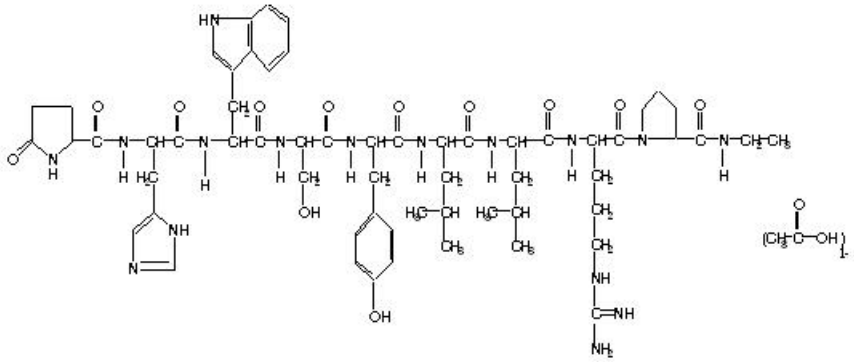
LEUPROLIDE ACETATE -
Genzyme Corporation

DESCRIPTION

Leuprolide Acetate Injection is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



Leuprolide Acetate Injection is a sterile, aqueous solution intended for subcutaneous injection. It is available in a 2.8 mL multiple-dose vial containing 5 mg/mL of leuprolide acetate, sodium chloride for tonicity adjustment, 9 mg/mL of benzyl alcohol as a preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

In humans, subcutaneous administration of single daily doses of leuprolide acetate results in an initial increase in circulation levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, continuous daily administration of leuprolide acetate results in decreased levels of LH and FSH in all patients. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to five years.

Leuprolide acetate is not active when given orally. Bioavailability by subcutaneous administration is comparable to that by intravenous administration. Leuprolide acetate has a plasma half-life of approximately three hours. The metabolism, distribution and excretion of leuprolide acetate in man have not been determined.

INDICATIONS AND USAGE

Leuprolide Acetate Injection is indicated in the palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient. In a controlled study comparing leuprolide acetate 1 mg/day given subcutaneously to DES (diethylstilbestrol), 3 mg/day, the survival rate for the two groups was comparable after two years treatment. The objective response to treatment was also similar for the two groups.

CONTRAINDICATIONS

A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature.[1]

Leuprolide Acetate Injection is contraindicated in women who are or may become pregnant while receiving the drug. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/600 to 1/6 the human dose) to rabbits, leuprolide acetate produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of leuprolide acetate in rabbits and with the highest dose in rats. The effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy.

WARNINGS

Isolated cases of worsening of signs and symptoms during the first weeks of treatment have been reported. Worsening of symptoms may contribute to paralysis with or without fatal complications.

PRECAUTIONS

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see "ADVERSE REACTIONS" section).

Patients with known allergies to benzyl alcohol, an ingredient of the drug's vehicle, may present symptoms of hypersensitivity, usually local, in the form of erythema and induration at the injection site.

Information for Patients:

See Information for Patients which appears after the"HOW SUPPLIED" section.

Laboratory Tests:

Response to leuprolide acetate should be monitored by measuring serum levels of testosterone and acid phosphatase. In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. Castrate levels were reached within two to four weeks and once attained were maintained for as long as drug administration continued. Transient increases in acid phosphatase levels occurred sometimes early in treatment. However, by the fourth week, the elevated levels usually decreased to values at or near baseline.

Drug Interactions:

None have been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). In mice no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Clinical and pharmacologic studies with leuprolide acetate and similar analogs have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks. However, no clinical studies have been conducted with leuprolide acetate to assess the reversibility of fertility suppression.

Pregnancy Category X. See "CONTRAINDICATIONS" section.

ADVERSE REACTIONS

In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. This transient increase was occasionally associated with a temporary worsening of signs and symptoms, usually manifested by an increase in bone pain (See"WARNINGS" section). In a few cases, a temporary worsening of existing hematuria and urinary tract obstruction occurred during the first week. Temporary weakness and paresthesia of the lower limbs have been reported in a few cases.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction which, if aggravated, may lead to neurological problems or increase the obstruction.

In a comparative trial of Leuprolide Acetate Injection versus DES, in 5% or more of the patients receiving either drug, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug related are excluded.

	Leuprolide Acetate (N=98)	**DES (N=101)**
	Number of Reports	
Cardiovascular System		
Congestive heart failure	1	5
ECG changes/ischemia	19	22
High blood pressure	8	5
Murmur	3	8
Peripheral edema	12	30

Phlebitis/thrombosis	2	10
Gastrointestinal System		
Anorexia	6	5
Constipation	7	9
Nausea/vomiting	5	17
Endocrine System		
*Decreased testicular size	7	11
*Gynecomastia/breast tenderness or pain	7	63
*Hot flashes	55	12
*Impotence	4	12
Hemic and Lymphatic System		
Anemia	5	5
Musculoskeletal System		
Bone pain	5	2
Myalgia	3	9
Central/Peripheral Nervous System		
Dizziness/lightheadedness	5	7
General pain	13	13
Headache	7	4
Insomnia/sleep disorders	7	5
Respiratory System		
Dyspnea	2	8
Sinus congestion	5	6
Integumentary System		
Dermatitis	5	8
Urogenital System		

Frequency/urgency	6	8
Hematuria	6	4
Urinary tract infection	3	7
Miscellaneous		
Asthenia	10	10
Physiologic effect of decreased testosterone		

In this same study, the following adverse reactions were reported in less than 5% of the patients on leuprolide acetate. *Cardiovascular System* --Angina, Cardiac arrhythmias, Myocardial infarction, Pulmonary emboli;*Gastrointestinal System*--Diarrhea, Dysphagia, Gastrointestinal bleeding, Gastrointestinal disturbance, Peptic ulcer, Rectal polyps; *Endocrine System* --Libido decrease, Thyroid enlargement; *Musculoskeletal System*--Joint pain; *Central/Peripheral Nervous System*--Anxiety, Blurred vision, Lethargy, Memory disorder, Mood swings, Nervousness, Numbness, Paresthesia, Peripheral neuropathy, Syncope/blackouts, Taste disorders;*Respiratory System*--Cough, Pleural rub, Pneumonia, Pulmonary fibrosis; *Integumentary System*--Carcinoma of skin/ear, Dry skin, Ecchymosis, Hair loss, Itching, Local skin reactions, Pigmentation, Skin lesions; *Urogenital System*--Bladder spasms, Dysuria, Incontinence, Testicular pain, Urinary obstruction; *Miscellaneous*--Depression, Diabetes, Fatigue, Fever/chills, Hypoglycemia, Increased BUN, Increased calcium, Increased creatinine, Infection/inflammation, Ophthalmologic disorders, Swelling (temporal bone).

The following additional adverse reactions have been reported with leuprolide acetate during other clinical trials and/or during postmarketing surveillance. Reactions considered as nondrug related by the treating physician are excluded.

Cardiovascular System --Hypotension, Transient ischemic attack/stroke; *Gastrointestinal System*--Hepatic dysfunction; *Endocrine System* --Libido increase; *Hemic and Lymphatic System*--Decreased WBC, Hemoptysis; *Musculoskeletal System*--Ankylosing spondylosis, Pelvic fibrosis; *Central/Peripheral Nervous System*--Hearing disorder, Peripheral neuropathy, Spinal fracture/paralysis; *Respiratory System*--Pulmonary infiltrate, Respiratory disorders; *Integumentary System*--Hair growth; *Urogenital System*--Penile swelling, Prostate pain; *Miscellaneous*--Hypoproteinemia, Hard nodule in throat, Weight gain, Increased uric acid.

OVERDOSAGE

In rats, subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials with leuprolide acetate, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

DOSAGE AND ADMINISTRATION

The recommended dose is 1 mg (0.2 mL or 20 unit mark) administered as a single daily subcutaneous injection. As with other drugs administered chronically by subcutaneous injection, the injection site should be varied periodically.

NOTE: As with all parenteral products, inspect container's solution for discoloration and particulate matter before each use.

HOW SUPPLIED

Leuprolide Acetate Injection is a sterile solution supplied in a 2.8 mL multiple-dose vial. It is available as a kit containing one multiple-dose vial of leuprolide acetate, 28 alcohol pads, and 14 disposable syringes.

Each 0.2 mL contains 1 mg of leuprolide acetate, sodium chloride for tonicity adjustment, 1.8 mg of benzyl alcohol as preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

NDC 49884-368-26

Store below 25°C (77 °F). Do not freeze.

Protect from light—retain in carton until contents are used.

REFERENCE

1. MacLeod TL, Eisen A, Sussman GL, et al: Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril*1987 Sept;48(3):500-502.

INFORMATION FOR PATIENTS

NOTE: Be sure to consult your physician with any questions you may have or for information about Leuprolide Acetate Injection and its use.

WHAT IS LEUPROLIDE ACETATE INJECTION?

Leuprolide Acetate Injection is chemically similar to gonadotropin releasing hormone (GnRH or LH-RH), a hormone which occurs naturally in your body.

Normally, your body releases small amounts of LH-RH and this leads to events which stimulate the production of sex hormones. However, when you inject Leuprolide Acetate Injection, the normal events that lead to sex hormone production are interrupted and testosterone is no longer produced by the testes.

Leuprolide acetate must be injected because, like insulin which is injected by diabetics, leuprolide acetate is inactive when taken by mouth.

If you were to discontinue the drug for any reason, your body would begin making testosterone again.

DIRECTIONS FOR USING LEUPROLIDE ACETATE INJECTION

1. Wash hands thoroughly with soap and water.

2. If using a new bottle for the first time, flip off the plastic cover to expose the gray rubber stopper. Wipe metal ring and rubber stopper with an alcohol wipe each time you use Leuprolide Acetate Injection. Check the liquid in the container. If it is not clear or has particles in it, DO NOT USE IT. Exchange it at your pharmacy for another container.

3. Remove outer wrapping from one syringe. Pull plunger back until the tip of the plunger is at the 0.2 mL or 20 unit mark.

4. Take cover off needle. Push the needle through the center of the rubber stopper on the Leuprolide Acetate Injection bottle.

5. Push the plunger all the way in to inject air into the bottle.

6. Keep the needle in the bottle and turn the bottle upside down. Check to make sure the tip of the needle is in the liquid. Slowly pull back on the plunger, until the syringe fills to the 0.2 mL or 20 unit mark.

7. Toward the end of a two-week period, the amount of Leuprolide Acetate Injection left in the bottle will be small. Take special care to hold the bottle straight and to keep the needle tip in liquid while pulling back on the plunger.

8. Keeping the needle in the bottle and the bottle upside down, check for air bubbles in the syringe. If you see any, push the plunger *slowly*in to push the air bubble back into the bottle. Keep the tip of the needle in the liquid and pull the plunger back again to fill to the 0.2 mL or 20 unit mark.

9. Do this again if necessary to eliminate air bubbles. Remove needle from bottle and lay syringe down. DO NOT TOUCH THE NEEDLE OR ALLOW THE NEEDLE TO TOUCH ANY SURFACE.

10. To protect your skin, inject each daily dose at a different body spot.

11. Choose an injection spot. Cleanse the injection spot with another alcohol wipe.

12. Hold the syringe in one hand. Hold the skin taut, or pull up a little flesh with the other hand, as you were instructed.

13. Holding the syringe as you would a pencil, thrust the needle all the way into the skin at a 90° angle.

14. Hold an alcohol wipe down on your skin where the needle is inserted and withdraw the needle at the same angle it was inserted.

15. Use the disposable syringe only once and dispose of it properly as you were instructed. Needles thrown into a garbage bag could accidentally stick someone. NEVER LEAVE SYRINGES, NEEDLES OR DRUGS WHERE CHILDREN CAN REACH THEM.

SOME SPECIAL ADVICE

- You may experience hot flashes when using Leuprolide Acetate Injection. During the first few weeks of treatment you may experience increased bone pain, increased difficulty in urinating, and less commonly but most importantly, you may experience the onset or aggravation of nerve symptoms. In any of these events, discuss the symptoms with your doctor.

- You may experience some irritation at the injection site, such as burning, itching or swelling. These reactions are usually mild and go away. If they do not, tell your doctor.

- Do not stop taking your injections because you feel better. You need an injection every day to make sure leuprolide acetate keeps working for you.

- If you need to use an alternate to the syringe supplied with Leuprolide Acetate Injection, insulin syringes should be utilized.

- When the drug level gets low, take special care to hold the bottle straight up and down and to keep the needle tip in liquid while pulling back on the plunger.
- Do not try to get every last drop out of the bottle. This will increase the possibility of drawing air into the syringe and getting an incomplete dose. Some extra drug has been provided so that you can withdraw the recommended number of doses.
- Tell your pharmacist when you will need Leuprolide Acetate Injection so it will be at the pharmacy when you need it.
- Store below 25 °C (77 °F). Do not store near a radiator or other very warm place. Do not freeze. Protect from light – retain in carton until contents are used.
- Do not leave your drug or hypodermic syringes where anyone can pick them up.
- Keep this and all other medications out of reach of children.

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